PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : G01N 21/31, A61B 5/00 G01N 33/48	A1	(11) International Publication Number: WO 92/17765 (43) International Publication Date: 15 October 1992 (15.10.92)

(21) International Application Number: PCT/GB92/00572

(22) International Filing Date: 30 March 1992 (30.03.92)

(30) Priority data:
9106672.0 28 March 1991 (28.03.91) GB

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(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: METHOD AND APPARATUS FOR GLUCOSE CONCENTRATION MONITORING

(57) Abstract

A test radiation source emits a radiation beam having a wavelength in the bandwidth 1500 nm to 1700 nm, and a reference radiation source emits a radiation beam having a wavelength in the bandwidth 1200 to 1400 nm. Both beams pass through a test medium of blood to a detector arranged to detect, and produce an output signal dependent on the intensity of radiation beams impinging thereon. Typically the beams are pulsed and the temperature of the test medium is elevated to provide improved operation and results.

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Method and Apparatus for Glucose Concentration Monitoring

This invention relates to a method and apparatus for measuring the concentration of glucose in an aqueous solution.

The brain uses glucose almost exclusively as an energy source, and it is therefore extremely important to maintain blood glucose levels within a very narrow range. Under normal conditions the levels of glucose in the blood stream are maintained in an elaborate series of mechanisms and feedback loops. These serve to counter fluctuations in glucose and restore it to the correct level.

In normal patients high levels of glucose trigger insulin release into the blood stream from the pancreas and conversely low levels suppress its release, thus regulating the normal blood glucose level.

Diabetes mellitus is caused by a lack of insulin in the patient which leads to a chronically raised blood glucose level causing unpleasant short term symptoms such as frequent urination and thirst, and more serious long term problems in the form of damage to the kidneys, blood vessels, nerves and eyes.

Low levels of blood glucose cause a condition known as hypoglycaemia which results in short term mental confusion, and, if prolonged, coma and even death.

A known method of detecting and treating diabetic patients involves the analysis of blood withdrawn from the patient. This involves the patient pricking a finger with a sterile lance to produce a sample of capillary blood which is placed on a test strip impregnated with appropriate chemicals to produce a colour change, the intensity of which is compared with a printed standard card. A more recent development has been a technique (EXACTECH Pen) which gives a digital readout of blood glucose concentration a few seconds after a sample has been placed on the disposable thin film printed sensor.

If diabetes is diagnosed, insulin may be prescribed. Since the glucose level in each individual is variable, in the absence of continuous measurements of blood glucose, it is impossible to give insulin which is appropriate at all times to the physiological need. As a consequence, diabetic patients still have periods of high blood glucose levels. On the other hand, administration of excess insulin can result in low blood glucose.

Near infrared spectrometric techniques are known for measuring the concentration of particular substances in blood. For example, European patent application 0160768 describes a reflectance technique using pre-selected test and reference wavelengths. U.S. patent 4655225 describes a technique utilising spectrophotometric analysis of near infra-red test wavelengths to ascertain the presence of glucose. Near infra-red absorption of glucose is described with peak wavelength for glucose adsorption of 2098nm and a reference wavelength of 1100nm. Also PCT patent application WO90/07905 describes a technique where 980nm is used as the peak wavelength for glucose detection.

The selection of the wavelength of the radiation is critical for the following reasons:

1. The concentration of glucose averages only about 0.1% by weight of blood serum. An accuracy of 50ppm is required for any meaningful measurement of glucose concentration.
2. Other components in the blood absorb in the near infra-red region and could interfere with the glucose measurement, e.g. the concentrations of serum proteins are significantly higher than glucose, therefore, compounding the interference problem.
3. Absorption measurements of aqueous solutions are difficult because of the strong background absorption of water. This strong absorption severely limits the application and use of a conventional spectrometer in solving this problem.

The fact that water is a major constituent of tissue is a significant factor in choosing the wavelength at which to measure the concentration of glucose in blood. Water exhibits strong absorption bands in the near infra-red with maxima around 1130nm, 1420nm and 1910nm. Transmission windows for water open at around 1250nm, 1600nm and 2150nm. Further water absorption increases with wavelengths. For these reasons the wavelength chosen should be as low as possible and should be within the transmission windows for water.

We have now devised an improved technique and apparatus for measuring the concentration of blood glucose. According to a first aspect of the invention, there is provided apparatus for determining the concentration of glucose in a test medium of blood, which apparatus comprises:

(a) a first radiation source for generating a first beam of electromagnetic radiation of a wavelength substantially in the bandwidth 1500 to 1700nm;

(b) a second radiation source for generating a second beam of electromagnetic radiation of a second wavelength in the bandwidth 1200 to 1400nm;

(c) detector means arranged to detect electromagnetic radiation from said first and second radiation beams; and

(d) means arranged to direct said first and second electromagnetic radiation beams along respective paths through a test medium of said blood to said detector means.

The detector means is spaced from the first and second radiation means such that the blood to be tested (i.e. the test medium) which may be contained in a transparent-walled container, or alternatively, in part of the body (such as a finger), which may be interposed between the detector means and first/second radiation sources.

Advantageously, the first wavelength is in the bandwidth 1547nm to 1577nm, and is more preferably of 1547 to 1557nm.

It is preferred that the second wavelength is in the bandwidth 1295nm to 1305nm, and is more preferably of wavelength substantially 1300nm.

It is preferred that pulsation means is provided for the apparatus, such that at least one of the radiation beams may be pulsed. Preferably, the pulsation means enables both the first and second radiation beams to be pulsed, advantageously alternately.

Pulsation of the beams enables high power radiation to be used, and thereby increases the ability of the radiation beams to penetrate sufficiently through the test medium to the detector means. This is particularly the case where the apparatus is used for <u>in vivo</u> measurements utilising for example a person's finger containing the test medium (i.e. blood).

It is preferred that the respective paths of the radiation beams are substantially rectilinear through the test medium. Advantageously the paths of the radiation beams are effectively co-linear through the test medium.

The first and second radiation sources may be laser devices (preferably monochromatic). More preferably, laser diodes are arranged to emit respective laser beams of the required frequency.

Alternatively, the radiation sources may be combined in a single laser (or laser diode) source arranged to emit two radiation beams (corresponding to the first and second radiation beams) of the required frequency.

The detector means may comprise a discrete detector for each radiation beams; however it is preferred that the detector means is in the form of a unitary detector arranged to detect radiation from both the first and second beams of electromagnetic radiation.

The detector means preferably produces electrical output signals dependent on the intensity of the electromagnetic radiation impinging on the detector representing the intensity of the first and second radiation means. Advantageously, signal processing and conditioning means is provided arranged to process the output signals from the detector means and provide a value corresponding to the difference in the intensities of the respective radiation beams impinging on the detector means, thereby enabling a value of glucose absorption (and hence glucose concentration) to be found. Preferably, the detector is in the form of a photodiode, for example, a germanium photodiode, and is preferably coupled via appropriate electrical circuitry to the signal processing and conditioning apparatus such that a value of glucose concentration in the blood may be obtained.

It is preferred that the apparatus further comprises heater means arranged to elevate the temperature of the blood under test. Advantageously, the heater means is capable of elevating the blood temperature to 40 degrees Celsius.

Typically collimator means is provided for the apparatus, arranged to direct the first and second electromagnetic radiation beams along their respective paths through the test medium.

The collimator means may comprise a lens and/or prism arrangement arranged to direct the radiation beams along effectively co-linear paths.

In a preferred embodiment, optical waveguides may comprise at least a part of the collimator means. In particular, in this embodiment optical fibre waveguides may be used in close side by side arrangement such that the first and second radiation beams effectively follow the same (i.e. co-linear) path through the test medium.

In an embodiment of the apparatus according to the first aspect of the invention, the apparatus is adapted for in vitro determination of glucose concentration of a sample of blood. In this embodiment, the apparatus preferably further comprises a walled receptacle within which the sample may be contained. The receptacle walls preferably comprise a transparent substance, and advantageously a spectrophotometric glass cuvette may be used. Advantageously, a cover is also provided for the receptacle, arrangeable to exclude ambient light from entering the receptacle.

In a second embodiment according to the first aspect of the invention, the apparatus is adapted for use in non-invasive measurement of glucose concentration. In this embodiment, it is preferred that a sleeve member suitable for receiving a finger of a patient is provided as a housing for at least some of the components of the apparatus, and particularly the detector means. Advantageously, the sleeve is also arranged to house the collimator means, and also the first and second radiation sources where practicable, e.g. where laser diodes are used.

According to a second aspect of the invention, there is provided a method of determining the concentration of glucose in a test medium of blood, which method comprises directing a first radiation beam of a wavelength substantially in the bandwidth 1500 to 1700nm along a first path from a source to radiation detection means; directing a second radiation beam of a wavelength substantially in the band width 1200 to 1400nm, along a second path from a source to said radiation detection means, said first and second paths passing through said test medium in a region intermediate said source(s) and said radiation detection means.

It is preferred that the respective paths of the radiation beams are rectilinear as they pass through the test medium, advantageously the respective paths of the radiation beams are effectively co-linear as they pass through the test medium.

It is preferred that at least one of the first and second radiation beams is pulsed such that an intermittent beam of radiation is provided. Preferably, both the first and second radiation beams are pulsed alternately.

Advantageously, the temperature of the blood is elevated, preferably to about 40 degrees Celsius, before, or during, determination of the glucose concentration by the method according to the invention.

The invention will now be further described in a particular embodiment, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 is a schematic representation of apparatus according to the invention which is suitable for carrying out the method according to the invention;

Figure 2 is a schematic plan view of part of the apparatus of Figure 1; and

Figure 3 is a schematic representation of alternative apparatus according to the invention.

Referring to the drawings, the apparatus generally designated 1 is arranged to determine the concentration of glucose in a sample of blood contained in a high precision spectrophotometric glass cuvette 2.

Two laser diodes 3, are driven by standard laser driver circuitry 4. Of the laser diodes 3 used in the apparatus, one is selected to emit a beam of wavelength of 1552nm (which is absorbed by glucose and therefore acts as the test beam), and one selected to emit a beam of wavelength of 1310nm (which is not absorbed by glucose and therefore acts as a reference beam).

The operating temperature of the laser diodes can be controlled by the use of a Peltier-driver 12. The operating temperature of the diodes can be varied to change to emitted wavelengths of the respective beams by $\pm$ 5nm. Accordingly the apparatus operates optimally at constant temperature.

The laser diodes 3 are mounted one either side of polished reflecting prism 5. Light emitted from each diode 3 is reflected by the prism 5 through a collimating lens 6. Thus prism 5 and collimating lens 6 comprise an optical system which directs and focuses the beams emitted from the laser diodes 3 such that they follow the same rectilinear path (i.e. the two paths are co-linear) throughout the blood sample in the glass cuvette 2.

The alignment of the respective laser diodes 3 with the optical system is controlled by XYZ axis Micropositioner 11.

Alternatively, the beams may be directed from respective laser diodes by means of fibre optic waveguides arranged in close side by side arrangement at their emitting ends. Since the diameter of the optical fibres would be of the order of 400 micrometres, the laser beams would follow effectively the same co-linear path.

Furthermore, the separate laser diodes 3 may be replaced by a single semi-conductor device such as a single diode arranged to emit separate beams of the required wavelength.

To ensure that the two beams emitted from respective laser diodes 3 are not superposed whilst following the same path best shown in Figure 2 through the blood sample, the laser diode drive circuitry 4 is arranged to supply power to each diode 3 cyclicly such that the respective laser beams emitted thereby are pulsed alternately. The pulsing of the beams enables higher intensity beams to be used than would ordinarily be possible with a "constant" beam, without causing damage to the structure of the blood. The ability to use high intensity beams ensures that the light beam travels right through the test sample in the glass cuvette 2.

The laser diodes used in this instrumentation may be pulsed with a duty cycle of 0.1 milliseconds, and a pulse duration of 4 microseconds. These parameters are dependent on laser diodes characteristics and may be modified accordingly.

A photodiode detector 7 is arranged adjacent the glass cuvette 2 to collect light from the laser beams which is transmitted through the blood sample in the glass cuvette 2. The photodiode detector may be a germanium diode; alternatively an Indium Gallium Arsenide detector may be used. The photodiode detector 7 produces an electrical output signal proportional to the intensity of light detected, and this signal is relayed via appropriate conventional electronic circuitry to signal processing and conditioning apparatus 8 arranged to give a digital output value related to the intensity of light detected by the photodiode detector 7.

In use, since the diodes 3 are pulsed alternately, the respective laser beams generated pass alternately along the same path through the blood sample contained in the glass cuvette 2. The light of the respective beams is therefore alternately transmitted to the photodiode detector 7 where alternate respective electrical output signals are generated.

The light beam of wavelength 1552nm is highly absorbed by glucose in solution in the blood sample, and therefore the transmitted light of this wavelength is related to the concentration of glucose within the blood sample. The light beam of wavelength 1310nm is not absorbed by glucose in solution in the blood sample, and therefore the intensity of this wavelength detected by the photodetector 7 relates to the "background" absorption of water and no other constituents the blood. Appropriate comparison and processing of these alternating respective output signals by the signal processing and conditioning apparatus 8 enables a value for glucose concentration in the blood sample to be obtained.

Unexpectedly, it was found that if the temperature of the blood in the cuvette was elevated to around 40°C, the amplitude of the light beams transmitted to the photodetector 7 increased considerably for both the test and the reference beam. This is extremely beneficial in terms of sensitivity of measurement of glucose concentration in the blood sample, and a cuvette heater 10 was therefore incorporated in the apparatus. However, to meaningfully compare sample with sample, the temperature at which the measurement is made has to be constant and identical in each case. Without this heating effect the resolution is not good enough to differentiate accurately and reproducibly between different glucose-containing samples within the ranges of clinical significance.

Referring to Figure 3, an alternative embodiment of apparatus is shown adapted for in vivo use. An electrically heated sleeve (or housing) 13 defines a finger receiving cavity 15 within which the patients finger 14 is received and elevated to a temperature of about 40°C. A single semi-conductor laser diode 3 is located in the sleeve 13 and emits the two radiation beams of the "test" and "reference" beam wavelengths (defined above) respectively. The beams penetrate and pass through the user's finger where they are received at the detector 7 which produces respective output signals which are then sent to appropriate signal processing apparatus (not shown) along appropriate circuitry 16. The laser diode 3 is connected to driver and pulsation apparatus (not shown) by appropriate circuitry 17.

CLAIMS:

1. Apparatus for determining the concentration of glucose in blood, which apparatus comprises:
   (a) a first radiation source for generating a first beam of electromagnetic radiation of a wavelength substantially in the bandwidth 1500 to 1700nm;
   (b) a second radiation source for generating a second beam of electromagnetic radiation of a second wavelength in the bandwidth 1200 to 1400nm;
   (c) detector means arranged to detect electromagnetic radiation from said first and second radiation beams; and
   (d) means arranged to direct said first and second electromagnetic radiation beams along respective paths through a test medium of said blood to said detector means.

2. Apparatus according to claim 1, wherein the respective paths of the radiation beams are substantially rectilinear through said test medium.

3. Apparatus according to claim 2, wherein the paths of the radiation beams are effectively co-linear through said test medium.

4. Apparatus according to any preceding claim, wherein pulsation means is provided for the apparatus, such that at least one of the radiation beams may be pulsed.

5. Apparatus according to claim 4, wherein both of the radiation sources may be pulsed.

6. Apparatus according to claims 4 or 5, wherein the pulsation means is arranged to pulse the first and second radiation beams alternately.

7. Apparatus according to any preceding claim, wherein the first radiation source is arranged to generate a wavelength in the band width 1547nm to 1577nm.

8. Apparatus according to any preceding claim, wherein the second radiation source is arranged to generate a wavelength in the bandwidth 1295nm to 1305nm.

9. Apparatus according to any preceding claim, wherein the first and second radiation sources are laser devices.

10. Apparatus according to claim 9, wherein the first and second laser devices are laser diodes.

11. Apparatus according to claims 9 or 10, wherein a single said laser device is provided to emit both the first and second radiation beams.

12. Apparatus according to any preceding claim, wherein the detector means is in the form of a unitary detector arranged to detect radiation from both the first and second beams of electromagnetic radiation.

13. Apparatus according to any preceding claim, wherein the detector means is arranged to produce an electrical output signal dependent on the intensity of the electromagnetic radiation impinging on the detector.

14. Apparatus according to claim 13, wherein the detector is a photodiode.

15. Apparatus according to any preceding claim, which further comprises heater means capable of elevating the temperature of the test medium.

16. Apparatus according to any preceding claim, wherein collimator means is provided arranged to direct the first and second radiation beams along their respective paths through the test medium.

17. Apparatus according to claim 16, wherein the collimator means comprises an optical lens and/or prism arrangement arranged to direct the first and second electromagnetic radiation beams along their respective paths.

18. Apparatus according to claim 16, wherein the collimator means comprises optical waveguide means.

19. Apparatus according to any preceding claim, which further comprises a walled receptacle within which the test sample may be contained.

20. Apparatus according to any of claims 1 to 18, which further comprises a sleeve member shaped and dimensioned to receive a finger of a patient.

21. Apparatus according to claim 20, wherein the sleeve member is adapted to house one or more of the radiation sources, detector and/or collimator means.

22. A method of determining the concentration of glucose in blood, which comprises directing a first radiation beam of a wavelength substantially in the bandwidth 1500 to 1700nm along a first path from a source to radiation detection means; directing a second radiation beam of a wavelength substantially in the band width 1200 to 1400nm, along a second path from a source to said radiation detection means, said first and second paths passing through a test medium in a region intermediate said source(s) and said detection means.

23. A method according to claim 22, wherein the respective paths of the radiation beams are rectilinear as they pass through the test medium.

24. A method according to claim 23, wherein the respective paths of the radiation beams are effectively co-linear as they pass through the test medium.

25. A method according to any of claims 22 to 24, wherein at least one of the first and second radiation beams is pulsed.

26. A method according to claim 25, wherein both the first and second radiation beams are pulsed.

27. A method according to any of claims 22 to 26, which further comprises elevating the temperature of the test medium.

28. A method according to claim 27, wherein the temperature of the test medium is elevated to about 40° Celsius.

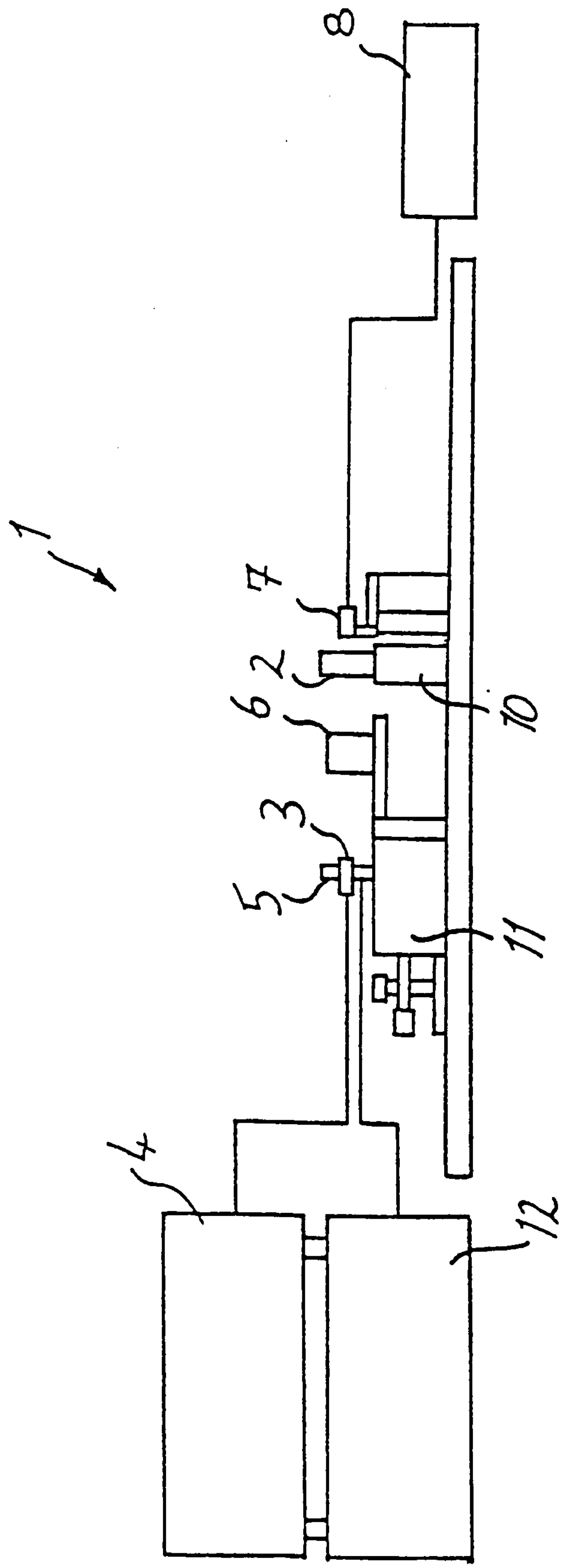


Figure 1

Figure 2

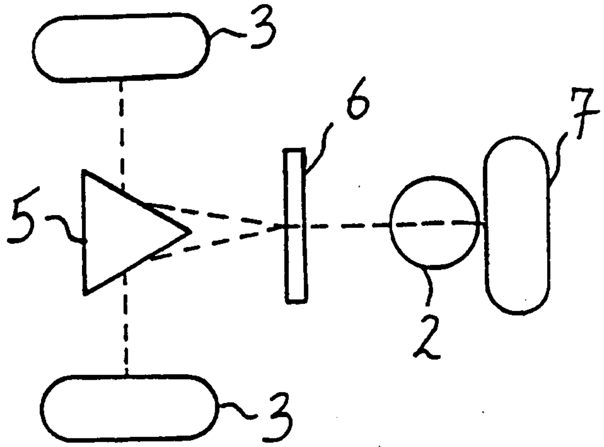
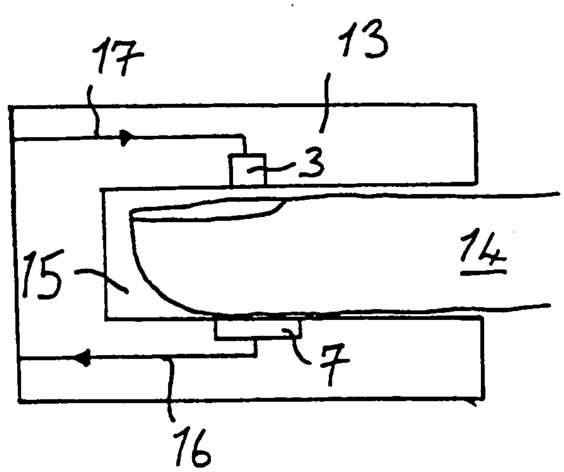


Figure 3



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/00572

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 G01N21/31; A61B5/00; G01N33/48

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	G01N ; A61B

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[o]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y A	EP,A,0 160 768 (BATTELLE MEMORIAL INSTITUTE) 13 November 1985 cited in the application see page 8, line 7 - page 14, line 30; claim 1; figures	1-15, 19-20, 22-28 16
Y A	WO,A,9 007 905 (FUTREX) 26 July 1990 cited in the application see page 7, line 5 - page 18, line 6; figures	1-15, 19-20, 22-28 21
P, Y P, A	WO,A,9 115 990 (INOMET) 31 October 1991 see page 3, line 25 - page 12, line 7; figures	15,27,28 1-14,18, 22-26

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[o] Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20 JULY 1992	28. 07. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	R.A.P. BOSMA

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A,4 882 492 (SCHLAGER) 21 November 1989 see column 3, line 46 - column 5, line 68; figures ---	1-3,7,8, 12-14, 22-24
A	EP,A,0 401 453 (BIOSENSORS TECHNOLOGY) 12 December 1990 see the whole document ---	1-14, 22-26
A	PATENT ABSTRACTS OF JAPAN vol. 8, no. 42 (P-256)(1479) 23 February 1984 & JP,A,58 193 438 (TOUA DENPA KOGYO K.K.) 11 November 1983 see abstract ---	1-3, 22-24

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200572 SA 57945

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 20/07/92
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0160768	13-11-85	CA-A-	1247397	27-12-88
		JP-B-	3047099	18-07-91
		JP-A-	60236631	25-11-85
WO-A-9007905	26-07-90	US-A-	5028787	02-07-91
		AU-A-	5042190	13-08-90
		EP-A-	0456716	21-11-91
		JP-A-	2191434	27-07-90
		US-A-	5086229	04-02-92
		US-A-	5068536	26-11-91
WO-A-9115990	31-10-91	US-A-	5115133	19-05-92
		AU-A-	7789391	11-11-91
		US-A-	5079421	07-01-92
US-A-4882492	21-11-89	None		
EP-A-0401453	12-12-90	None		

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82